DRAFT PROPOSAL FOR AEGL-1 FOR AMMONIA

5 Min.	10 Min.	30 Min.	1 Hour	4 Hours	8 Hours
50 ppm 35 mg/m^3	50 ppm 35 mg/m^3	50 ppm 35 mg/m^3	50 ppm 35 mg/m^3	50 ppm 35 mg/m^3	50 ppm 35 mg/m^3

Rationale

50 ppm:

- Nasal dryness was reported by 2/10 subjects exposed for 5 minutes (Industrial Bio-Test Lab., 1973).
- Moderate irritation (grade 2) was reported by 4/6 subjects, faint or just perceptible irritation by 1/6, and irritation was not detectable by 1/6 exposed for 10 minutes (MacEwen et al., 1970).
- The greatest response to a 2-hour exposure was nuisance irritation and general discomfort was perceptible (Verberk, 1977).

Rationale

30-32 ppm:

Faint irritation was reported by 2/6 subjects, not detectable by 3/6, and no response by 1/6 (MacEwen et al., 1970).

- Nasal dryness was reported by 1/10 subjects (Industrial Bio-Test Lab., 1973).

Intraspecies Uncertainty Factor and Rationale: UF = 1

Atopic subjects did not respond differently from non-atopic to a brief nasal exposure to 100 ppm.

- A child recovered completely from exposure to ammonia concentrations that left the mother with permanent lung damage.

GEORGE V. ALEXEEFF, PH.D., D.A.B.T.
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Comments:

AEGL-1

I suggest that the derivation of the AEGL-1 values be revised to improve clarity and understanding. The AEGL-1 derivation (page 38, line 29) states: "The AEGL-1 is based upon slight eye irritation noted in the Hastings et al. (1986) study during a 30-minute exposure to 400 ppm mixed xylenes." The derivation does not state if this is the NOAEL or the LOAEL for the AEGL-1. Later in the paragraph it states that "an intraspecies uncertainty factor of 3 was applied because the toxic effect (slight irritation) was less severe than that defined for the AEGL-1 tier (notable discomfort)." This statement suggests the starting point is the NOAEL. The document should be revised to indicate that the starting point, a 30-minute exposure to 400 ppm mixed xylenes, is the NOAEL for the AEGL-1 level. The document should further indicate that at and below the AEGL-1 slight eye irritation may occur since the AEGL-1 does not protect against this effect. Furthermore, the document should identify the LOAEL for AEGL-1. Finally, the derivation requires a different justification for the uncertainty factor of 3 since choosing the NOAEL is the standing operating procedure and not a justification for a specific uncertainty factor. The summary tables should also be revised to indicate that the endpoint is the "NOAEL for notable comfort (or the specific effect)."

AEGL-2

The AEGL-2 is "based upon poor coordination resulting when rats were exposed to 1300 ppm mixed xylenes for 4 hours (Carpenter et al., 1975)." Thus the document is suggesting that the poor coordination is a NOAEL for AEGL-2 effects and consequently poor coordination is an AEGL-1 effect. If this is the case the document should clearly indicate that exposure to 1300 ppm mixed xylenes for 4 hours is a NOAEL for AEGL-2 effects as described in the standard operating procedures. The summary tables should also indicate that it is a NOAEL for AEGL-2 effects. Furthermore the document needs to identify the AEGL-2 effect of concern, that is, the LOAEL for AEGL-2.

In the derivation section for AEGL-2 (page 40, line 5), the document indicates: "An interspecies uncertainty factor of 1 was applied because rats receive a greater systemic dose of inhaled xylene as compared to humans." No justification is provided for this statement. Interspecies uncertainty is operationally divided into two factors, tissue dose (toxicokinetics) and tissue response (pharmacodynamics). Each of these factors is understood to contribute an uncertainty of approximately 3-fold. The document makes a toxicokinetic statement that rats receive a greater dose of xylenes than humans; this statement requires additional justification in document. However, there is no discussion regarding the responsiveness of rat tissue to effects of xylenes in comparison to humans. In fact the limited data available suggest that humans may be more sensitive. Carpenter (1975) reported that exposure to 690 ppm for 15 minutes produced dizziness in 4 of 6 individuals. This appears to be an AEGL-2 effect that occurs at a concentration at least

2-fold below that of rats. Consequently, the use of an interspecies uncertainty factor does not appear to be supported by the available data.

On page 4, (line 20), the document explains why the Carpenter (1975) data were not used for the derivation of the AEGL-2 by stating: "If one were to use the highest exposure concentration ... and apply the intraspecies uncertainty factor of 3, one obtains a value of 230 ppm. This concentration is supposed to represent a concentration at which exposed individuals could experience irreversible or other serious, long-lasting adverse health effects, or have an impaired ability to escape." This statement suggests that the AEGL-2 effect would be expected to be present at 230 ppm, the calculated AEGL-2. However, the AEGL-2 definition on page i states it is the concentration "above which it is predicted" that the effect would occur. Consequently, the effect would be expected to occur above 230 ppm, not *at* 230 ppm. If the document had identified the AEGL-2 LOAEL, then the effect would be expected at the LOAEL. Thus, further discussion regarding the use of the Carpenter (1975) study as the starting point for the AEGL-2 appears warranted.

AEGL-3

Greater clarity would be helpful in the tables and derivation of the AEGL-3. In the summary table on page vii, the endpoint for AEGL-3 provided is "rats exposed to 2800 ppm for 4 hours exhibited prostration followed by a full recovery." The relevant effect of the experiment is that this the highest non-lethal dose. I suggest that the following be added: "This exposure constituted the NOAEL for lethality in rats." Further, I request that this clarification be added to all similar tables and text in the document and appendices.

The justification for an interspecies uncertainty factor of 1 appears to be insufficient. The justification states: "An interspecies uncertainty factor of 1 was applied because rats receive a greater systemic dose of inhaled xylene as compared to humans." As discussed above, the justification may address toxicokinetics, however, it does not address the responsiveness of rat tissue to effects of xylenes in comparison to humans. Additional justification of this uncertainty factor appears warranted.

Response: The suggested changes have been made in the Executive Summary, the Table of AEGL values, and sections 5.3, 6.3, and 7.3.

INTERNATIONAL UNION, UAW

Comments:

Investigation of AEGL-1 Health Effects of Xylene
The U.S. Environmental Protection Agency (EPA) states that AEGL-1 values are airborne concentrations above which members of the general public could experience notable discomfort, irritation or other reversible non-disabling health effects. Studies used as evidence for setting AEGL-1 values should clearly state the methods used to determine whether or not there were health effects. The study by Ogata (1970) looked only at excretion of by-products after controlled xylene exposure, not health effects. It cannot be assumed that there were no health effects at the exposure levels reported in the study because the authors did not look for any health effects. AEGL documents are likely to be used by emergency personnel without access to the original studies. For this reason, the description of human studies and their use as evidence should be as scientifically accurate as possible.

Response: The Ogata et al. (1970) study indeed looked at excretion of metabolites in humans after controlled xylene exposure. However, they also assessed systolic and diastolic blood pressure, pulse rate, flicker value, and reaction time in all volunteers at the beginning and the end of exposures. No effects were observed in these health endpoints.

AEGL-2 Derivation
AEGL-2 values are airborne concentrations above which members of the general public could experience impaired ability to escape, irreversible health effects, or other serious long-lasting health effects. In the reference to multiple human studies at the end of Section 6.3 – AEGL-2 Derivation, it would be better to state that either "no disabling effects" were found or only "mild effects were observed," rather than stating that these studies found "no adverse effects". If this statement were changed, it would be appropriate to use the Ogata study to support the AEGL-2 values.

Response
The sentence:

> **"However, a number of studies demonstrate that this concentration has no adverse effects upon exposed individuals: no adverse effects were observed following exposure to 100 or 200 ppm m- or p-xylene for 3 or 7 hours (Ogata et al., 1970); 200 ppm m-xylene for 4 hours (Savolainen et al., 1981; Seppalainen et al., 1985), or 200 ppm for 5.5 hours (Laine et al., 1993)."**

will be changed to

> **"However, a number of studies demonstrate that only minor sensory irritation is observed following exposure to 100 or 200 ppm m- or p-xylene for 3 or 7 hours (Ogata et al., 1970); 200 ppm m-xylene for 4 hours (Savolainen et al., 1981; Seppalainen et al., 1985), or 200 ppm for 5.5 hours (Laine et al., 1993)."**

Ogata et al. (1970) shows no effect on the ability to escape at 200 ppm for 3 or 7 hours and thus supports the AEGL-2 value. However, it is not appropriate to use this study to derive the AEGL-2 value as 200 ppm is far below the threshold for effects on the central nervous system.

AEGL-2 10 minute value

The AEGL Committee for Xylene proposes to set a 10-minute AEGL-2 xylene exposure value of 990 parts per million (ppm). In the Carpenter (1975) study, the highest exposure was 690 ppm for 15 minutes. At that concentration, 4 of the 6 volunteers reported slight dizziness. One of those experienced a slight loss of balance. The severity of these health effects is less than that specified by the AEGL-2 definition. Unfortunately, there are no studies that examined health effects at higher exposures. For this reason, it would be imprudent to set the AEGL-2 value above the 690 ppm level, at which mild health effects have been demonstrated.

Response: The effects noted in Carpenter (1975) would not impair escape. It is therefore appropriate to set an AEGL-2 value above this exposure concentration.

*In setting the 10 minute AEGL-2 value, the committee used blood data * from three studies of resting subjects. Two of these studies however, show that blood Xylene concentrations after exercise are two to three times higher **. Exercising subjects may be more similar to people experiencing a chemical emergency than resting ones. Blood xylene concentrations from exercising subjects rather than resting ones are more appropriate for setting the value.*

Response: As noted in Appendix B, an assumption was made that the inhalation volume and frequency were constant across individuals. To provide sufficient protectiveness for persons experiencing a chemical emergency, a value two standard deviations below the mean was used as the starting point to derive the AEGL-2 and AEGL-3 values for 10 and 30 minutes. In addition, an uncertainty factor of 3 was applied for intraspecies variability.

AEGL-3 10 minute value

The AEGL-3 value is the airborne concentration of a substance above which it is predicted that members of the general public could experience life threatening health effects or death. To set this value, the committee used blood data from the same studies used to set the AEGL-2 10 minute value. Again, blood xylene concentrations from exercising subjects rather than resting ones are more appropriate for setting the value. In order to account for varying degrees of vulnerability among different people in setting the AEGL-3 values for exposures lasting 1-8 hours, the committee divides by three so that exposure below the AEGL value will not do serious harm to someone who is three times more vulnerable than most people. However, in setting AEGL-3 values below one hour, the committee reduces the value only by 18%. This does not provide an adequate margin of safety.

Response: As noted in Appendix B, an assumption was made that the inhalation volume and frequency were constant across individuals. To provide sufficient protectiveness for persons experiencing a chemical emergency, a value two standard

deviations below the mean was used as the starting point to derive the AEGL-2 and AEGL-3 values for 10 and 30 minutes. In addition, an uncertainty factor of 3 was applied for intraspecies variability.

* See Table 11, p.37 of Proposed Acute Exposure Guideline Levels for Xylene

** Laine (1993) found that, at 200 ppm, there was more than a two fold increase after 10 minutes of exercise (17 vs. 43 μmol/l). Hake (1981) found that, at 150 ppm, there was almost a 3-fold increase after 11 minutes of exercise (4.6 to 12.5 ppm;). In addition Gamberale (1978) found a 3.7 fold difference in alveolar air at 300 ppm exposure for 30 minutes when comparing exercising subjects to resting exposure.

CLEAN CHANNEL ASSOCIATION:

Comments:

I am concerned with some of the AEGL values recommended by the AEGL Committee as they approach the Lower Explosive Level (LEL). The emergency response community has used 10%LEL as their action levels for many years. This safety margin takes into account the error of the instruments and the conditions under which these measurements are taken. The Incident Commander is reminded to re-evaluate any response actions that entry team members would take when levels are above the action level; using higher levels may place teams in dangerous environments without considering other options. I request the committee remove any value from the summary tables that are above 50% of the LEL.This will prevent emergency responders from erroneously assuming that these levels would not have potential lethal results. When derived values are above 50%of the LEL, the recommended numbers should not be within the summary tables but instead put in a footnote. Levels above 10%of the LEL can be within the tables with a footnote similar to that used for some of the published chemicals. Both Methyl Ethyl Ketone (MEK)and Xylene have this situation.

For Xylene, the 10-minute AEGL-3 value of 2,100 ppm is above 10% of the LEL for all forms of Xylene (o-xylene (9,000 ppm) and m-and p-xylene LEL (11,000 ppm)) and should be noted in all summary tables. Since the other AEGL 3 values are between 10% of the LEL for o-xylene and m-and p-xylene (11,000 ppm) an additional note should be added to enable emergency responders to draw their own conclusions.

Response: The suggested change has been made.

MICHIGAN DEQ

Comments:

The discussion in the Federal Register proposed rule and technical support document on xylenes was very good and quite complete. Many of the relevant toxicity studies were reviewed. However, this reviewer believes the documentation could be improved by including additional discussion concerning why an AEGL value is not developed for each of the individual xylene isomers. That is, discussion should include why one AEGL value should apply to all of the isomers and the mixture. For example, it could be mentioned that the individual isomers and mixture are expected to have similar toxicity, and metabolic pathways of each isomer proceeds via the same mechanism. Therefore, the proposed xylene AEGL values apply to any of the xylene isomers or a mixture of xylene isomers.

> **Response: The description of the studies investigating the potential differences in the toxicity of the individual isomers that was included in the IRIS Xylenes document will be added to the AEGL document (see Appendix, this document), with the statement:**
>
> **"Only a limited number of studies were found in the searched literature comparing the toxicity of the individual xylene isomers. Although differences did exist among the isomers, no consistent, significant differences in the potency of the isomers following oral or inhalation exposure were identified. Additionally, metabolism of each isomer proceeds via the same pathways. Therefore, the proposed xylene AEGL values apply to any of the xylene isomers or a mixture of xylene isomers."**

An additional comment concerns the use of the modeling to obtain AEGL 2 & 3 value for various shorter time periods. The selection of the NONMEM program for extrapolation to 10 and 30 minute exposure concentrations could use more discussion in the technical support document. Appendix B should describe in a general overview this software program for those unfamiliar with NONMEM. The following was obtained from the GloboMax® website, and could be paraphrased in the document to serve as an overview of NONMEM:

"GloboMax® LLC is pleased to announce its agreement with the Regents of University of California at San Francisco to become the licensor of NONMEM, the "gold standard" software package for Population Pharmacokinetic/ Pharmacodynamic data analyses. Since 1979, the NONMEM Project at the University of California at San Francisco has been concerned with the development of data analysis techniques and exportable software for estimating the parameters of nonlinear mixed effects (statistical regression-type) models. These techniques are particularly useful when the data are population pharmacokinetic/pharmacodynamic data, and when there are only a few PK/PD measurements from some individuals sampled from the population, or when the regression design varies considerably between individuals."

> **Response: If it is decided to continue to use the AEGL-2 and -3 values obtained by NOMEN, a reference to the software vendor wil be provided.**

AMERICAN CHEMISTRY COUNCIL

Comments:

The American Chemistry Council Toluene and Xylene Panel (the "Panel") appreciates the opportunity to submit the following comments on tehpropesed Acute Exposure Guideline Limits (AEGLs) for xylenes. The panel represents the major U.S. manufacturers of xylenes, which includes mixed xylenes, p-xylene, o-xylene, and m-xylene.

The Panel has reviewed proposed AEGL values presented in the July 18, 2003, Federal Register notice and the supporting document - the "Public Draft" of the Proposed AEGLs for Xylene May 2002 - that provide the detailed toxicology review and derivation of these proposed AEGLs. The toxicology review presented in the AEGL documentation appears to be thorough, organized, and well summarized. Further, the recommended critical studies and health endpoints used in deriving the AEGL-1, -2, and -3 values appear to be appropriate. The applied uncertainty factors and extrapolation for the time periods appear to be consistent with the established guidelines published in the SOP for Developing AEGLs for Hazardous Chemicals.

The Panel does, however, believe that the proposed AEGLs and the corresponding documentation should be revised to clearly indicate that these AEGLs apply to both mixed xylenes as well as to the individual isomers of xylene and any combination thereof. The toxicology assessment clearly covers the data on all three of the individual isomers in addition to data on mixed (technical) xylenes. Recent reviews by EPA for the IRIS database and by the OECD for it SIDS program have concluded that the individual isomers and mixed xylenes can be treated similarly for hazard and risk assessment. The toxicology and metabolism data presented in the proposed AEGL document also supports this conclusion.

Response: Same comment as that provided to MDEQ:

The description of the studies investigating the potential differences in the toxicity of the individual isomers that was included in the IRIS Xylenes document will be added to the AEGL document (see Appendix, this document), with the statement:

"Only a limited number of studies were found in the searched literature comparing the toxicity of the individual xylene isomers. Although differences did exist among the isomers, no consistent, significant differences in the potency of the isomers following oral or inhalation exposure were identified. Additionally, metabolism of each isomer proceeds via the same pathways. Therefore, the proposed xylene AEGL values apply to any of the xylene isomers or a mixture of xylene isomers."

The individual xylene isomers are produced primarily for use as intermediates in the production of other chemicals. As the Executive Summary does not address these applications, the Panel

suggest that the following passage, taken from the recent xylenes SIDS profile (May 2003), be included:

> *The primary use of the individual isomers is as chemical intermediates. Almost all o-xylene produced in the U.S. is consumed in the manufacture of phthalic anhydride. Other minor uses include the use of o-xylene as a feedstock in the production of bactericides, soybean herbicides, and dyes. Most m-xylene is used as a chemical intermediate in the production of isophthalic acid. Small amount of m-xylene are also consumed in the production of meta-tolic acid, isophthalonitrile, and other compounds, Almost all U.S. production of p-xylene is consumed in the manufacture of dimethyl terephthalate (DMT) and terephthalic acid (TPA), which are used in the production of polyester fiber and plastics.*

Response: This can be added.

Appendix - The description of the studies investigating the potential differences in the toxicity of the individual isomers

Moser et al. (1985) evaluated the effects of the individual xylene isomers and a commercial xylene mixture on operant responding and motor performance in CD-1 male albino mice following 30-minute static inhalation exposures. The minimally effective concentration for disruption of operant performance was 1400 ppm for all isomers, with an EC_{50} (concentration producing half-maximal decreases in response rate) of 6176, 5179, or 5611 ppm for m-xylene, o-xylene, and p-xylene, respectively. The operant response was biphasic, with concentrations of 1400 to 2400 ppm producing increased rates of response, and a concentration of 7000 ppm suppressing the response rate and also producing gross ataxia and prostration. The minimally effective concentrations for the inverted screen test were 3000 ppm for m- and o-xylene, and 2000 ppm for p-xylene, while the EC_{50} values for performance on the inverted screen test were 3790, 3640, and 2676 ppm for m-xylene, o-xylene, and p-xylene, respectively. Motor ability was recovered approximately 5 to 15 minutes after exposure. The study authors concluded that there was no consistent, significant difference in the potency of the individual isomers. While o-xylene exhibited a more potent effect on operant behavior, p-xylene more severely affected motor performance.

In a study by Molnár et al. (1986), motility was assessed in groups of eight, CFY white, male rats following exposure by inhalation for 4 hours to at least six concentrations each of m-xylene, o-xylene, or p-xylene (individual concentrations not provided). Exposure to 130 to 1500 ppm m-xylene and 400 to 1500 ppm p-xylene resulted in a concentration-related increase in group motility, while exposure to 150 to 1800 ppm o-xylene resulted in a slight depression of activity. At higher concentrations, however, activity was decreased in all groups, with the minimum narcotic concentration for the three isomers reported as 2180 ppm for o-xylene, 2100 ppm for m-xylene, and 1940 ppm for p-xylene.

Korsak et al. (1990) found that o-xylene more severely affected motor performance. Groups of ten, male Wistar rats were exposed to approximately 3000 ppm o-, m-, or p-xylene for six hours, with rotarod performance measured before and after termination of the exposure. The results of the testing given in terms of the number of failures/number of tested animals was as follows: o-xylene at average concentration of 3027 ppm was 19/20; m-xylene at average concentration of 3093 ppm was 6/20; p-xylene at average concentration of 3065 ppm was 1/20.

Condie et al. (1988) did not find any significant differences in the toxicity of the individual isomers in an experiment in which Sprague-Dawley rats were administered m-, o-, or p-xylene orally by gavage in corn oil for 10 consecutive days at doses of 0, 250, 1000, or 2000 mg/kg/day. Two female rats receiving the high-dose of p-xylene died and deaths were attributed to treatment. Male rats receiving 2000 mg/kg/day of each isomer had statistically lower body weights (88-94% of controls), while the body weights of high-dose females were not affected. Males and females receiving 2000 mg/kg/day of each isomer had statistically elevated liver weights and/or liver to body weight ratios (ranging from 128-148% of controls). Certain treatment groups also had decreased spleen or thymus weights. No treatment-related effects were observed in hematology,

clinical chemistry, or urinalysis parameters. The authors concluded that there were no significant differences in the toxicity of the individual isomers.

To address the potential for the 3 isomers to cause maternal or developmental toxicity, Ungváry et al. (1980) exposed groups of 15-30 pregnant, CFY rats to air containing measured concentrations of 35, 350, or 700 ppm of o-, m-, or p-xylene continuously during GD 7-14. Dams were sacrificed on GD 21. For a complete description of this study, the reader is referred to Section 4.3.2.2. Unfortunately, the usefulness of this study is limited because much of the actual data were not provided and the analyses of developmental toxicity was based on fetuses as the experimental unit instead of litters. The general conclusion is that m-xylene was the most toxic to the dams, while fetal toxicity varied with the isomer; for example, m-xylene resulted in decreased number of mean implantations/dam, p-xylene resulted in increased post implantation loss and corresponding decreased litter size, and all concentration of p-xylene and the highest concentration of o-xylene resulted in increased fetal incidence of skeletal retardation.

Fang et al. (1996) determined the Minimum Alveolar Concentration (MAC; the concentration that produces anesthesia, i.e. lack of movement, in 50% of those exposed) of the individual isomers in rats. The MAC of o-, m-, and p-xylene was 0.00118 ± 0.00009, 0.00139 ± 0.00010, and 00.00151 ± 0.0007 atm, respectively, with a difference of MAC values of less than 30% among the isomers.